Supplementary Information

Supplementary Methods

Data on clinical progress were collected on days 1, 3, 6 and 9 of admission and, if applicable, on the day of admission to critical care, as were data on interim outcome status at day 28 and final outcome (discharged alive/palliative discharge/in-hospital death) when that occured.

Variables

Baseline vital signs were used to calculate a Paediatric Early Warning Score (PEWS) which provided a measure of severity of illness at presentation.[1] In addition to the variables used for comorbidities in our original report, we also included a neurodevelopmental comorbidity category which included children and young people (CYP) with learning disability, autism spectrum disorders and attention deficit hyperactivity disorder.[2] Oxygen delivered by high-flow nasal cannulae was assigned as "high flow support" which is available in critical care environments and on some wards. CYP admitted for >5 days before testing for SARS-CoV-2 infection were categorised as potential hospital acquired infection.

Length of stay

Length of stay was calculated from date of assessment in hospital for SARS-CoV-2 infection and date of discharge (where this was recorded) and was available for patients who had a recorded discharge by 28 days.

Age

Age was calculated based on date of birth and date of assessment in hospital for SARS-CoV-2 infection.

Indices of multiple deprivation (IMD)

IMD scores were derived from postal codes for usual residence transcribed from hospital records. IMD quintile 1 represents the most deprived and quintile 5 the least deprived.

Critical care

Paediatric intensive care units (PICUs) are dedicated care settings providing the highest level of critical care for children and young people, who usually need invasive mechanical ventilation or support for two or more organ systems with a higher nurse to patient ratio. PICUs are usually located in regional tertiary centres or specialised hospitals. Paediatric high dependency units (HDUs) are for patients needing close monitoring and therapies for single organ system support, usually without invasive ventilation. HDUs are provided at tertiary hospitals and most district general hospitals.

Duplicates

Each child is represented once in the dataset. In cases where the child was readmitted, the admission with the highest level of care was retained. If readmissions required the same level of care, the earliest admission was retained. Where the child was transferred from one participating site to another during the same episode of care, their data were considerred as one admission, retaining the first available vital signs and laboratory results and recording the highest level of treatments they had received.

Criteria for diagnosis of MIS-C

The case report form contained a Y/N variable for multisystem inflammatory syndrome in children (MIS-C) also known as paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). We also adjusted the World Health Organisation (WHO) preliminary case definition for MIS-C, as previously described[2] and searched free text in case report forms for "MIS-C", "PIMS-TS" and "IVIg" (intravenous immunoglobulin). Patients identified using these three approaches were collated and sites contacted directly to clarify the diagnosis and to collect further details. Patients with pathogenic bacteria identified in blood or cerebrospinal fluid cultures and those with a diagnosis of appendicitis were censored from the MIS-C subgroup.

Incidental SARS-CoV-2

Coded "yes":

- Patients where SARS-CoV-2 was noted to be incidental in free text.
- Patients with alternative reasons for admission, where free text notes no SARS-CoV-2 symptoms or asymptomatic.
- Patients where there is a clear primary reason for admission unrelated to any infection symptoms in free text e.g. overdose, road traffic accident.
- Patients where there is a clear primary reason for admission which relates to a specific focal infection not thought to be associated with SARS-CoV-2 e.g. septic arthritis, eczema herpeticum.

Coded "no / unknown":

- No mention of other reason for admission in free text, no mention of asymptomatic or incidental finding
- Patient came to hospital for another reason (eg pre admission screen) but had SARS-CoV-2 symptoms and was admitted for this

Patients who had been coded "yes" for other reason for admission, but where it was not clear whether SARS-CoV-2 symptoms also contributed to presentation. For example:

- Appendicitis.
- Diabetic ketoacidosis.
- Systemic infection related admissions, where co-infection could be present.

Other reason for admission

Coded "yes"

Patients where free text includes reference to another acute condition which could have contributed to admission. This includes but is not limited to:

- Fractures, burns and other injuries.
- Eating disorder, self-harm, drug overdose, psychosis (note where free text states only depression or anxiety this was considered chronic, and not an alternative reason for admission unless stated otherwise).
- Surgical admissions including appendicitis.
- New presentation of type 1 diabetes.
- Neonatal jaundice.
- Patients admitted in labour or for elective caesarean section.

Patients where free text includes reference of admission related to a chronic condition. This includes, but is not limited to:

- Exacerbation of inflammatory bowel syndrome.
- Diabetic ketoacidosis in known diabetic.
- Elective admissions for diagnostic investigations.
- Elective admissions for surgical procedures or chemotherapy.

Coded "no / unknown"

Patients where free text includes reference to acute symptoms/presentation which could also represent symptoms of SARS-CoV-2. Examples:

- Febrile convulsions.
- Seizures in known epilepsy.
- Acute exacerbation of asthma.
- Gastroenteritis.

Missing data

Capacity to enrol into the current study was limited by staff availability, especially during admission surges research staff were redeployed to clinical activities. We did not impute missing data. All

patients were admitted at least two weeks prior to the date of data extraction to minimise missing data. Denominators differ between analyses owing to incomplete data recorded for some variables. The research team undertook data cleaning and source verification to ensure the data extracted and analysed were as accurate as possible.

Supplementary Results

Assessment of potential sources of bias

In total, 764 CYP were admitted during the first wave (17th January to 31st July 2020) and 1,280 during the second wave (1st August 2020 to 31st January 2021) across a total of 187 sites of which 23 had access to an onsite paediatric intensive care unit (PICU) (*Supplementary Figure C* and *Supplementary Table A*). As reporting to ISARIC is not mandatory, we examined whether sites with onsite PICUs reported more CYP in one wave than another, which might bias the severity of illness in reported patients. 118 hospitals reported paediatric patients to ISARIC in both the first and second waves, 34 more reported in the first wave only and 35 in the second wave only. The proportion of patients reported from hospitals with access to an onsite PICU did not differ between the waves (37.0% (283/764) in the first wave vs 35.5% (455/1280, p = 0.53) in the second wave).

We then compared the number of CYP reported to ISARIC against the numbers of local SARS-CoV-2 cases identified by Pillar 1 and 2 testing by Public Health England across NHS regions (*Supplementary Figure D*). In the ISARIC dataset, regional peaks were seen in the Midlands in November 2020 and in London in December 2020 which closely mirrored those reported by Public Health England at the same time points, indicating that ISARIC also captured localised SARS-CoV-2 peaks across the UK.[3]

Supplementary Tables

Wave	Hospitals	Patients	Onsite PICU
First only	34	99	2
First and Second	118	1747	20
Second only	35	198	1

***Supplementary Table A**. Comparison of the number of sites reporting to ISARIC in the first and second waves against the number of patients reporting and whether the hospital had an on-site PICU.*

		First	Second	p
Total N (%)		665 (41.1)	952 (58.9)	
History of fever	No	148 (22.3)	311 (32.7)	<0.001
	Yes	491 (73.8)	544 (57.1)	
	(Missing)	26 (3.9)	97 (10.2)	
Cough	No	353 (53.1)	519 (54.5)	0.056
	Yes	269 (40.5)	320 (33.6)	
	(Missing)	43 (6.5)	113 (11.9)	
Cough: with sputum production	No	486 (73.1)	663 (69.6)	0.516
	Yes	40 (6.0)	46 (4.8)	
	(Missing)	139 (20.9)	243 (25.5)	
Sore throat	No	398 (59.8)	558 (58.6)	0.183
	Yes	59 (8.9)	106 (11.1)	
	(Missing)	208 (31.3)	288 (30.3)	
Runny nose (Rhinorrhoea)	No	438 (65.9)	616 (64.7)	0.423
	Yes	84 (12.6)	135 (14.2)	
	(Missing)	143 (21.5)	201 (21.1)	
Ear pain (Otalgia)	No	433 (65.1)	634 (66.6)	0.809
	Yes	11 (1.7)	19 (2.0)	
	(Missing)	221 (33.2)	299 (31.4)	
Wheezing	No	508 (76.4)	712 (74.8)	0.607
	Yes	53 (8.0)	66 (6.9)	
	(Missing)	104 (15.6)	174 (18.3)	
Muscle aches (Myalgia)	No	390 (58.6)	586 (61.6)	0.337
	Yes	51 (7.7)	62 (6.5)	
	(Missing)	224 (33.7)	304 (31.9)	
Joint pain (Arthralgia)	No	420 (63.2)	609 (64.0)	0.213
	Yes	18 (2.7)	39 (4.1)	
	(Missing)	227 (34.1)	304 (31.9)	
Fatigue / Malaise	No	331 (49.8)	496 (52.1)	0.471
	Yes	162 (24.4)	220 (23.1)	
	(Missing)	172 (25.9)	236 (24.8)	

		First	Second	p
Shortness of breath (Dyspnea)	No	406 (61.1)	574 (60.3)	0.174
	Yes	185 (27.8)	221 (23.2)	
	(Missing)	74 (11.1)	157 (16.5)	
Lower chest wall indrawing	No	475 (71.4)	699 (73.4)	0.196
	Yes	41 (6.2)	44 (4.6)	
	(Missing)	149 (22.4)	209 (22.0)	
Headache	No	375 (56.4)	544 (57.1)	0.690
	Yes	66 (9.9)	104 (10.9)	
	(Missing)	224 (33.7)	304 (31.9)	
Altered consciousness / confusion	No	516 (77.6)	716 (75.2)	0.803
	Yes	42 (6.3)	54 (5.7)	
	(Missing)	107 (16.1)	182 (19.1)	
Seizures	No	539 (81.1)	729 (76.6)	0.951
	Yes	37 (5.6)	52 (5.5)	
	(Missing)	89 (13.4)	171 (18.0)	
Abdominal pain	No	363 (54.6)	544 (57.1)	0.219
	Yes	126 (18.9)	158 (16.6)	
	(Missing)	176 (26.5)	250 (26.3)	
Vomiting / Nausea	No	377 (56.7)	553 (58.1)	0.336
	Yes	206 (31.0)	269 (28.3)	
	(Missing)	82 (12.3)	130 (13.7)	
Diarrhoea	No	467 (70.2)	666 (70.0)	0.374
	Yes	107 (16.1)	133 (14.0)	
	(Missing)	91 (13.7)	153 (16.1)	
Conjunctivitis	No	498 (74.9)	703 (73.8)	0.581
	Yes	28 (4.2)	33 (3.5)	
	(Missing)	139 (20.9)	216 (22.7)	
Skin rash	No	481 (72.3)	693 (72.8)	0.096
	Yes	96 (14.4)	106 (11.1)	
	(Missing)	88 (13.2)	153 (16.1)	
Lymphadenopathy	No	490 (73.7)	721 (75.7)	0.009
	Yes	27 (4.1)	17 (1.8)	
	(Missing)	148 (22.3)	214 (22.5)	
Bleeding (Haemorrhage)	No	542 (81.5)	775 (81.4)	0.091
	Yes	14 (2.1)	9 (0.9)	
	(Missing)	109 (16.4)	168 (17.6)	

Supplementary Table B. *Presenting symptoms by wave, with CYP with asymptomatic / incidental SARS-CoV-2 infections excluded.*

		First	Second	p
Total N (%)		665 (41.1)	952 (58.9)	
Any comorbidity	No/Unknown	367 (55.2)	571 (60.0)	0.062
	Yes	298 (44.8)	381 (40.0)	
Prematurity	No	160 (24.1)	206 (21.6)	0.159
	Yes	43 (6.5)	38 (4.0)	
	(Missing)	462 (69.5)	708 (74.4)	
Neurological	No	570 (85.7)	770 (80.9)	0.526
	Yes	67 (10.1)	102 (10.7)	
	(Missing)	28 (4.2)	80 (8.4)	
Neurodisability	No	577 (86.8)	785 (82.5)	0.900
	Yes	32 (4.8)	41 (4.3)	
	(Missing)	56 (8.4)	126 (13.2)	
Neurodevelopmental	No	590 (88.7)	773 (81.2)	0.648
	Yes	27 (4.1)	41 (4.3)	
	(Missing)	48 (7.2)	138 (14.5)	
Respiratory	No	599 (90.1)	832 (87.4)	0.378
	Yes	34 (5.1)	37 (3.9)	
	(Missing)	32 (4.8)	83 (8.7)	
Asthma	No	590 (88.7)	787 (82.7)	0.149
	Yes	49 (7.4)	87 (9.1)	
	(Missing)	26 (3.9)	78 (8.2)	
Cardiac	No	597 (89.8)	835 (87.7)	0.048
	Yes	40 (6.0)	34 (3.6)	
	(Missing)	28 (4.2)	83 (8.7)	
Gastrointestinal	No	614 (92.3)	847 (89.0)	0.444
	Yes	22 (3.3)	23 (2.4)	
	(Missing)	29 (4.4)	82 (8.6)	
Haematology / Oncology / Immunology	No	588 (88.4)	815 (85.6)	0.373
	Yes	47 (7.1)	53 (5.6)	
	(Missing)	30 (4.5)	84 (8.8)	
Obesity	No	607 (91.3)	808 (84.9)	0.949
	Yes	19 (2.9)	27 (2.8)	
	(Missing)	39 (5.9)	117 (12.3)	
Malnutrition	No	626 (94.1)	835 (87.7)	0.169
	Yes	5 (0.8)	15 (1.6)	
	(Missing)	34 (5.1)	102 (10.7)	
Diabetes	No	621 (93.4)	844 (88.7)	0.477
	Yes	17 (2.6)	17 (1.8)	
	(Missing)	27 (4.1)	91 (9.6)	
Other endocrine	No	607 (91.3)	805 (84.6)	0.542
	Yes	10 (1.5)	9 (0.9)	
	(Missing)	48 (7.2)	138 (14.5)	

		First	Second	p
Genetic	No	593 (89.2)	781 (82.0)	0.983
	Yes	24 (3.6)	33 (3.5)	
	(Missing)	48 (7.2)	138 (14.5)	
Renal	No	623 (93.7)	846 (88.9)	0.603
	Yes	14 (2.1)	24 (2.5)	
	(Missing)	28 (4.2)	82 (8.6)	
Metabolic	No	615 (92.5)	807 (84.8)	0.351
	Yes	2 (0.3)	7 (0.7)	
	(Missing)	48 (7.2)	138 (14.5)	
Rheumatology	No	631 (94.9)	858 (90.1)	0.182
	Yes	5 (0.8)	15 (1.6)	
	(Missing)	29 (4.4)	79 (8.3)	
Other	No	576 (86.6)	772 (81.1)	0.274
	Yes	42 (6.3)	43 (4.5)	
	(Missing)	47 (7.1)	137 (14.4)	

Supplementary Table C. *Comparison of comorbidities across the two waves, CYP with asymptomatic or incidental SARS-CoV-2 excluded.*

		First	Second	p
Total N (%)		764 (37.4)	1280 (62.6)	
Any comorbidity	No/Unknown	408 (53.4)	738 (57.7)	0.065
	Yes	356 (46.6)	542 (42.3)	
Prematurity	No	175 (22.9)	229 (17.9)	0.173
	Yes	49 (6.4)	47 (3.7)	
	(Missing)	540 (70.7)	1004 (78.4)	
Neurological	No	652 (85.3)	1066 (83.3)	0.939
	Yes	78 (10.2)	126 (9.8)	
	(Missing)	34 (4.5)	88 (6.9)	
Neurodisability	No	660 (86.4)	1084 (84.7)	0.162
	Yes	37 (4.8)	44 (3.4)	
	(Missing)	67 (8.8)	152 (11.9)	
Neurodevelopmental	No	674 (88.2)	1011 (79.0)	1.000
	Yes	33 (4.3)	49 (3.8)	
	(Missing)	57 (7.5)	220 (17.2)	
Respiratory	No	689 (90.2)	1146 (89.5)	0.101
	Yes	38 (5.0)	43 (3.4)	
	(Missing)	37 (4.8)	91 (7.1)	
Asthma	No	679 (88.9)	1090 (85.2)	0.266
	Yes	53 (6.9)	104 (8.1)	
	(Missing)	32 (4.2)	86 (6.7)	
Cardiac	No	686 (89.8)	1141 (89.1)	0.046
	Yes	44 (5.8)	47 (3.7)	
	(Missing)	34 (4.5)	92 (7.2)	
Gastrointestinal	No	706 (92.4)	1160 (90.6)	0.323
	Yes	24 (3.1)	30 (2.3)	
	(Missing)	34 (4.5)	90 (7.0)	
Haematology / Oncology / Immunology	No	676 (88.5)	1116 (87.2)	0.296
	Yes	53 (6.9)	72 (5.6)	
	(Missing)	35 (4.6)	92 (7.2)	
Obesity	No	698 (91.4)	1112 (86.9)	0.781
	Yes	20 (2.6)	36 (2.8)	
	(Missing)	46 (6.0)	132 (10.3)	
Malnutrition	No	715 (93.6)	1145 (89.5)	0.092
	Yes	7 (0.9)	24 (1.9)	
	(Missing)	42 (5.5)	111 (8.7)	
Diabetes	No	714 (93.5)	1158 (90.5)	0.413
	Yes	18 (2.4)	22 (1.7)	
	(Missing)	32 (4.2)	100 (7.8)	
Other endocrine	No	697 (91.2)	1050 (82.0)	0.368
	Yes	10 (1.3)	10 (0.8)	
	(Missing)	57 (7.5)	220 (17.2)	

		First	Second	p
Genetic	No	680 (89.0)	1022 (79.8)	0.798
	Yes	27 (3.5)	38 (3.0)	
	(Missing)	57 (7.5)	220 (17.2)	
Renal	No	712 (93.2)	1162 (90.8)	0.762
	Yes	19 (2.5)	28 (2.2)	
	(Missing)	33 (4.3)	90 (7.0)	
Metabolic	No	705 (92.3)	1053 (82.3)	0.330
	Yes	2 (0.3)	7 (0.5)	
	(Missing)	57 (7.5)	220 (17.2)	
Rheumatology	No	724 (94.8)	1176 (91.9)	0.211
	Yes	6 (0.8)	18 (1.4)	
	(Missing)	34 (4.5)	86 (6.7)	
Other	No	637 (83.4)	938 (73.3)	0.319
	Yes	73 (9.6)	127 (9.9)	
	(Missing)	54 (7.1)	215 (16.8)	

Supplementary Table D. *Comparison of comorbidities for the whole cohort (i.e. includes asymptomatic or incidental SARS-CoV-2) across the two waves.*

	Total N		First	Second	p
Total N (%)			764 (37.4)	1280 (62.6)	
Antibiotic medication	1883 (92.1)	No	231 (30.2)	557 (43.5)	<0.001
		Yes	502 (65.7)	593 (46.3)	
		(Missing)	31 (4.1)	130 (10.2)	
Antiviral	1885 (92.2)	No	680 (89.0)	1100 (85.9)	0.215
		Yes	47 (6.2)	58 (4.5)	
		(Missing)	37 (4.8)	122 (9.5)	
Maximal steroid therapy	1820 (89.0)	None	598 (78.3)	955 (74.6)	<0.001
		Oral	38 (5.0)	144 (11.2)	
		IV	45 (5.9)	40 (3.1)	
		(Missing)	83 (10.9)	141 (11.0)	
Maximum respiratory support	1974 (96.6)	No respiratory support	551 (72.1)	979 (76.5)	<0.001
		Supplemental oxygen	69 (9.0)	123 (9.6)	
		High flow support	36 (4.7)	37 (2.9)	
		Non-invasive	38 (5.0)	31 (2.4)	
		Invasive	59 (7.7)	51 (4.0)	
		(Missing)	11 (1.4)	59 (4.6)	
ICU/HDU admission	1972 (96.5)	No	620 (81.2)	1007 (78.7)	1.000
		Yes	132 (17.3)	213 (16.6)	
		(Missing)	12 (1.6)	60 (4.7)	
Inotrope	1856 (90.8)	No	673 (88.1)	1102 (86.1)	<0.001
		Yes	52 (6.8)	29 (2.3)	
		(Missing)	39 (5.1)	149 (11.6)	
Total PEWS	1920 (93.9)	Median (IQR)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.0)	<0.001
PEWS over 2	1920 (93.9)	No	391 (51.2)	751 (58.7)	<0.001
		Yes	349 (45.7)	429 (33.5)	
		(Missing)	24 (3.1)	100 (7.8)	
Length of stay	1727 (84.5)	Median (IQR)	2.0 (1.0 to 6.0)	2.0 (1.0 to 4.0)	<0.001

Supplementary Table F. *Comparison of treatments received by children by wave across the whole cohort (i.e. includes asymptomatic and incidental SARS-CoV-2). ICU = intensive care unit, HDU = high dependency unit. PEWS = Paediatric Early Warning Score at presentation.*

	Total N		First	Second	p
Total N (%)			49 (53.8)	42 (46.2)	
Antibiotic medication	83 (91.2)	No	4 (8.2)	1 (2.4)	0.644
		Yes	45 (91.8)	33 (78.6)	
		(Missing)	0 (0.0)	8 (19.0)	
Maximal steroid therapy	72 (79.1)	None	12 (24.5)	15 (35.7)	0.200
		Oral	2 (4.1)	3 (7.1)	
		IV	26 (53.1)	14 (33.3)	
		(Missing)	9 (18.4)	10 (23.8)	
IVIg	91 (100.0)	No	8 (16.3)	17 (40.5)	0.018
		Yes	41 (83.7)	25 (59.5)	
Immunomodulator	89 (97.8)	No	41 (83.7)	37 (88.1)	0.537
		Yes	7 (14.3)	4 (9.5)	
		(Missing)	1 (2.0)	1 (2.4)	
Maximum respiratory support	91 (100.0)	No respiratory support	22 (44.9)	24 (57.1)	0.458
		Supplemental oxygen	3 (6.1)	5 (11.9)	
		High flow support	4 (8.2)	2 (4.8)	
		Non-invasive	8 (16.3)	3 (7.1)	
		Invasive	12 (24.5)	8 (19.0)	
ICU/HDU admission	89 (97.8)	No	13 (26.5)	15 (35.7)	0.359
		Yes	36 (73.5)	25 (59.5)	
		(Missing)	0 (0.0)	2 (4.8)	
Inotrope	91 (100.0)	No	23 (46.9)	22 (52.4)	0.676
		Yes	26 (53.1)	20 (47.6)	
Total PEWS	91 (100.0)	Median (IQR)	5.0 (2.0 to 6.0)	4.0 (2.0 to 6.0)	0.273
PEWS over 2	91 (100.0)	No	14 (28.6)	15 (35.7)	0.505
		Yes	35 (71.4)	27 (64.3)	
Length of stay	67 (73.6)	Median (IQR)	8.5 (5.8 to 12.0)	6.0 (4.0 to 10.0)	0.031

Supplementary Table G. *Treatments received by children with MIS-C by wave. ICU = intensive care unit, HDU = high dependency unit, PEWS = Paediatric Early Warning Score at presentation, IQR = interquartile range.*

	Total N		Ward-level care	Critical care	p
Total N (%)			1300 (84.0)	248 (16.0)	
Age	1548 (100.0)	<1 mth	90 (6.9)	23 (9.3)	<0.001
		>1mth <1 y	372 (28.6)	27 (10.9)	
		1-4 y	205 (15.8)	41 (16.5)	
		5-9 y	145 (11.2)	38 (15.3)	
		10-14 y	198 (15.2)	68 (27.4)	
		15-19 y	290 (22.3)	51 (20.6)	
Licenced vaccine available	1548 (100.0)	No (<= 11 years)	847 (65.2)	146 (58.9)	0.069
		Yes (>= 12 years)	453 (34.8)	102 (41.1)	
Sex at Birth	1546 (99.9)	Male	695 (53.5)	138 (55.6)	0.590
		Female	603 (46.4)	110 (44.4)	
		(Missing)	2 (0.2)	0 (0.0)	
Ethnicity	1341 (86.6)	White	697 (53.6)	85 (34.3)	<0.001
		Black	74 (5.7)	25 (10.1)	
		South Asian	173 (13.3)	47 (19.0)	
		Other ethnic minority	184 (14.2)	56 (22.6)	
		(Missing)	172 (13.2)	35 (14.1)	
IMD quintile	1432 (92.5)	1 (most deprived)	449 (34.5)	72 (29.0)	0.385
		2	263 (20.2)	35 (14.1)	
		3	190 (14.6)	30 (12.1)	
		4	153 (11.8)	34 (13.7)	
		5 (least deprived)	179 (13.8)	27 (10.9)	
		(Missing)	66 (5.1)	50 (20.2)	
Potential hospital acquired SARS-CoV-2	1548 (100.0)	No	1256 (96.6)	227 (91.5)	<0.001
		Yes	44 (3.4)	21 (8.5)	
PEWS over 2	1511 (97.6)	No	737 (56.7)	81 (32.7)	<0.001
		Yes	531 (40.8)	162 (65.3)	
		(Missing)	32 (2.5)	5 (2.0)	
Any comorbidity	1548 (100.0)	No/Unknown	764 (58.8)	112 (45.2)	<0.001
		Yes	536 (41.2)	136 (54.8)	
Comorbidity count	1548 (100.0)	Median (IQR)	0.0 (0.0 to 1.0)	1.0 (0.0 to 1.0)	<0.001
Length of stay	1358 (87.7)	Median (IQR)	2.0 (1.0 to 3.2)	8.0 (4.0 to 12.0)	<0.001

***Supplementary Table H**. Demographics and key clinical characteristics of children stratified by critical care admission (excluding asymptomatic or incidental SARS-CoV-2 infections but including those with MIS-C). IMD = indices of multiple deprivtation. PEWS = Paediatric Early Warning Score at presentation.*

		Ward-level care	Critical care	p
Total N (%)		1300 (84.0)	248 (16.0)	
Any comorbidity	No/Unknown	764 (58.8)	112 (45.2)	<0.001
	Yes	536 (41.2)	136 (54.8)	
Prematurity	No	343 (26.4)	22 (8.9)	<0.001
	Yes	57 (4.4)	21 (8.5)	
	(Missing)	900 (69.2)	205 (82.7)	
Neurological	No	1136 (87.4)	197 (79.4)	<0.001
	Yes	121 (9.3)	46 (18.5)	
	(Missing)	43 (3.3)	5 (2.0)	
Neurodisability	No	1151 (88.5)	204 (82.3)	0.008
	Yes	53 (4.1)	20 (8.1)	
	(Missing)	96 (7.4)	24 (9.7)	
Neurodevelopmental	No	1165 (89.6)	190 (76.6)	0.589
	Yes	56 (4.3)	11 (4.4)	
	(Missing)	79 (6.1)	47 (19.0)	
Respiratory	No	1203 (92.5)	221 (89.1)	0.003
	Yes	49 (3.8)	21 (8.5)	
	(Missing)	48 (3.7)	6 (2.4)	
Asthma	No	1149 (88.4)	220 (88.7)	0.467
	Yes	111 (8.5)	25 (10.1)	
	(Missing)	40 (3.1)	3 (1.2)	
Cardiac	No	1204 (92.6)	221 (89.1)	0.001
	Yes	49 (3.8)	23 (9.3)	
	(Missing)	47 (3.6)	4 (1.6)	
Gastrointestinal	No	1227 (94.4)	227 (91.5)	0.001
	Yes	28 (2.2)	16 (6.5)	
	(Missing)	45 (3.5)	5 (2.0)	
Haematology / Oncology / Immunology	No	1169 (89.9)	226 (91.1)	1.000
	Yes	84 (6.5)	16 (6.5)	
	(Missing)	47 (3.6)	6 (2.4)	
Obesity	No	1181 (90.8)	226 (91.1)	0.041
	Yes	33 (2.5)	13 (5.2)	
	(Missing)	86 (6.6)	9 (3.6)	
Malnutrition	No	1217 (93.6)	237 (95.6)	1.000
	Yes	16 (1.2)	3 (1.2)	
	(Missing)	67 (5.2)	8 (3.2)	
Diabetes	No	1222 (94.0)	235 (94.8)	0.813
	Yes	28 (2.2)	6 (2.4)	
	(Missing)	50 (3.8)	7 (2.8)	
Other endocrine	No	1207 (92.8)	197 (79.4)	0.306
	Yes	14 (1.1)	4 (1.6)	
	(Missing)	79 (6.1)	47 (19.0)	

		Ward-level care	Critical care	p
Genetic	No	1175 (90.4)	193 (77.8)	0.843
	Yes	46 (3.5)	8 (3.2)	
	(Missing)	79 (6.1)	47 (19.0)	
Renal	No	1223 (94.1)	240 (96.8)	0.498
	Yes	32 (2.5)	4 (1.6)	
	(Missing)	45 (3.5)	4 (1.6)	
Metabolic	No	1212 (93.2)	201 (81.0)	0.623
	Yes	9 (0.7)	0 (0.0)	
	(Missing)	79 (6.1)	47 (19.0)	
Rheumatology	No	1247 (95.9)	234 (94.4)	<0.001
	Yes	10 (0.8)	10 (4.0)	
	(Missing)	43 (3.3)	4 (1.6)	
Other	No	1145 (88.1)	194 (78.2)	0.146
	Yes	78 (6.0)	7 (2.8)	
	(Missing)	77 (5.9)	47 (19.0)	

***Supplementary Table I**. Comorbidities of CYP stratified by critical care admission excluding asymptomatic or incidental SARS-CoV-2 infections but including those with MIS-C.*

		Ward-level care	Critical care	OR (univariable)	OR (multivariable)	OR (multilevel)
Wave	First	526 (87.1)	78 (12.9)	-	-	-
	Second	746 (87.3)	109 (12.7)	0.99 (0.72-1.35, p=0.926)	0.91 (0.61-1.39, p=0.674)	0.95 (0.61-1.48, p=0.823)
Age	>1mth <1 y	371 (93.2)	27 (6.8)	-	-	-
	<1 mth	90 (79.6)	23 (20.4)	3.51 (1.91-6.41, p<0.001)	8.14 (3.73-18.29, p<0.001)	9.27 (4.03-21.31, p<0.001)
	1-4 y	199 (84.7)	36 (15.3)	2.49 (1.47-4.25, p=0.001)	2.38 (1.14-5.07, p=0.022)	2.28 (1.05-4.93, p=0.036)
	5-9 y	133 (88.1)	18 (11.9)	1.86 (0.98-3.46, p=0.053)	1.46 (0.58-3.55, p=0.413)	1.43 (0.56-3.63, p=0.456)
	10-14 y	189 (83.6)	37 (16.4)	2.69 (1.60-4.59, p<0.001)	2.97 (1.42-6.43, p=0.005)	2.90 (1.33-6.32, p=0.007)
	15-19 y	290 (86.3)	46 (13.7)	2.18 (1.33-3.63, p=0.002)	2.51 (1.26-5.24, p=0.011)	2.72 (1.29-5.71, p=0.008)
Sex at Birth	Male	674 (86.9)	102 (13.1)	-	-	-
	Female	596 (87.5)	85 (12.5)	0.94 (0.69-1.28, p=0.706)	0.95 (0.63-1.44, p=0.811)	0.99 (0.64-1.53, p=0.969)
Ethnicity	White	683 (90.6)	71 (9.4)	-	-	-
	Black	71 (82.6)	15 (17.4)	2.03 (1.07-3.65, p=0.022)	1.05 (0.42-2.36, p=0.913)	1.00 (0.40-2.47, p=0.996)
	South Asian	167 (81.1)	39 (18.9)	2.25 (1.46-3.42, p<0.001)	1.17 (0.63-2.10, p=0.611)	1.35 (0.70-2.60, p=0.367)
	Other ethnic minority	181 (82.3)	39 (17.7)	2.07 (1.35-3.15, p=0.001)	2.53 (1.51-4.21, p<0.001)	2.53 (1.47-4.35, p=0.001)
IMD quintile	1 (most deprived)	438 (89.9)	49 (10.1)	-	-	-
	2	256 (90.8)	26 (9.2)	0.91 (0.54-1.48, p=0.705)	0.97 (0.53-1.73, p=0.918)	1.00 (0.54-1.86, p=0.993)
	3	187 (89.9)	21 (10.1)	1.00 (0.57-1.70, p=0.989)	1.10 (0.58-2.02, p=0.763)	1.24 (0.64-2.41, p=0.526)
	4	151 (86.8)	23 (13.2)	1.36 (0.79-2.29, p=0.253)	1.68 (0.87-3.16, p=0.115)	1.84 (0.92-3.71, p=0.087)
	5 (least deprived)	175 (88.8)	22 (11.2)	1.12 (0.65-1.89, p=0.668)	1.13 (0.57-2.16, p=0.728)	1.30 (0.63-2.66, p=0.477)
Number of comorbidities	0	744 (92.7)	59 (7.3)	-	-	-
	1	336 (82.8)	70 (17.2)	2.63 (1.82-3.81, p<0.001)	4.03 (2.45-6.76, p<0.001)	3.87 (2.28-6.56, p<0.001)
	2+	192 (76.8)	58 (23.2)	3.81 (2.56-5.66, p<0.001)	4.25 (2.40-7.56, p<0.001)	4.04 (2.22-7.35, p<0.001)
PEWS over 2	No	725 (91.8)	65 (8.2)	-	-	-
	Yes	515 (81.5)	117 (18.5)	2.53 (1.84-3.52, p<0.001)	5.17 (3.29-8.36, p<0.001)	5.11 (3.16-8.27, p<0.001)

Supplementary Table J. *Multivariable analysis of factors associated with admission to critical care unit (excluding asymptomatic and incidental SARS-CoV-2 infections, and patients with Multisystem inflammatory syndrome in children (MIS-C)). Row percentages. IMD = Index of multiple deprivation. PEWS = Paediatric Early Warning Score at presentation. Odds ratios (OR) and 95% confidence intervals are presented.*

	Total N		No/Unknown Comorbidity	Comorbidity present	p
Total N (%)			938 (58.0)	679 (42.0)	
Age at assessment (Years)	1617 (100.0)	Median (IQR)	2.0 (0.2 to 12.9)	9.9 (1.9 to 15.3)	<0.001
Age	1617 (100.0)	<1 mth	91 (9.7)	31 (4.6)	<0.001
		>1mth <1 y	307 (32.7)	100 (14.7)	
		1-4 y	145 (15.5)	111 (16.3)	
		5-9 y	89 (9.5)	102 (15.0)	
		10-14 y	136 (14.5)	148 (21.8)	
		15-19 y	170 (18.1)	187 (27.5)	
Licenced vaccine available	1617 (100.0)	No (≤11 y)	660 (70.4)	372 (54.8)	<0.001
		Yes (≥ 12 y)	278 (29.6)	307 (45.2)	
Sex at Birth	1613 (99.8)	Male	496 (52.9)	367 (54.1)	0.745
		Female	438 (46.7)	312 (45.9)	
		(Missing)	4 (0.4)	0 (0.0)	
Ethnicity	1385 (85.7)	White	468 (49.9)	334 (49.2)	0.114
		Black	49 (5.2)	56 (8.2)	
		South Asian	136 (14.5)	97 (14.3)	
		Other ethnic minority	147 (15.7)	98 (14.4)	
		(Missing)	138 (14.7)	94 (13.8)	
IMD quintile	1491 (92.2)	1 (most deprived)	311 (33.2)	231 (34.0)	0.912
		2	182 (19.4)	128 (18.9)	
		3	140 (14.9)	91 (13.4)	
		4	110 (11.7)	85 (12.5)	
		5 (least deprived)	124 (13.2)	89 (13.1)	
		(Missing)	71 (7.6)	55 (8.1)	
Potential hospital acquired SARS-CoV-2	1617 (100.0)	No	919 (98.0)	631 (92.9)	<0.001
		Yes	19 (2.0)	48 (7.1)	
Total PEWS	1518 (93.9)	Median (IQR)	2.0 (1.0 to 4.0)	2.0 (1.0 to 5.0)	0.014
PEWS over 2	1518 (93.9)	No	471 (50.2)	351 (51.7)	0.315
		Yes	380 (40.5)	316 (46.5)	
		(Missing)	87 (9.3)	12 (1.8)	
Length of stay	1368 (84.6)	Median (IQR)	2.0 (1.0 to 3.0)	3.0 (1.0 to 7.0)	<0.001

Supplementary Table K. *Demographics and key clinical characteristics of CYP stratified by comorbidity (patients with asymptomatic or incidental SARS-CoV-2 infections excluded). Column percentages by sub-group. IMD = Indices of multiple deprivation. PEWS= Paediatric Early Warning Score at presentation. IQR = Interquartile range*

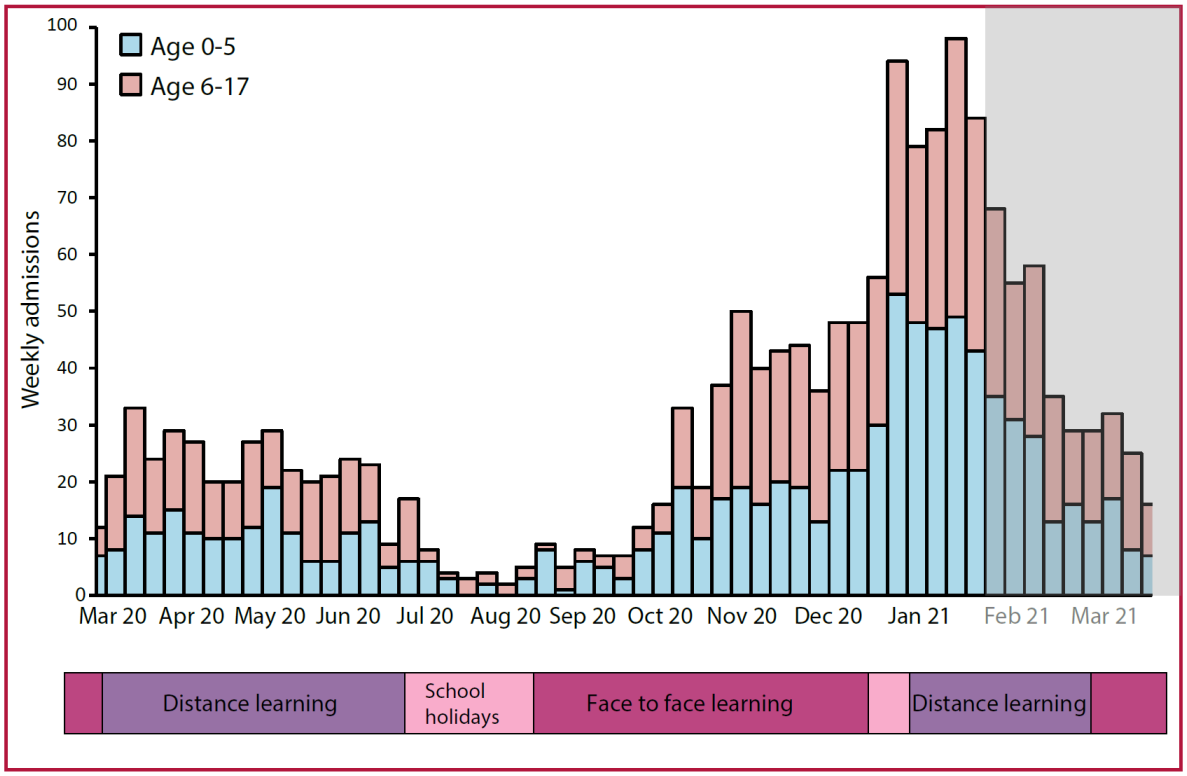
	Total N		No/Unknown Comorbidity	Comorbidity present	p
Total N (%)			863 (56.6)	663 (43.4)	
Antibiotic medication	1394 (91.3)	No	297 (34.4)	215 (32.4)	0.058
		Yes	464 (53.8)	418 (63.0)	
		(Missing)	102 (11.8)	30 (4.5)	
Antiviral	1385 (90.8)	No	719 (83.3)	579 (87.3)	0.008
		Yes	35 (4.1)	52 (7.8)	
		(Missing)	109 (12.6)	32 (4.8)	
Maximal steroid therapy	1350 (88.5)	None	693 (80.3)	468 (70.6)	<0.001
		Oral	49 (5.7)	102 (15.4)	
		IV	8 (0.9)	30 (4.5)	
		(Missing)	113 (13.1)	63 (9.5)	
Maximum respiratory support	1459 (95.6)	No respiratory support	701 (81.2)	418 (63.0)	<0.001
		Supplemental oxygen	53 (6.1)	106 (16.0)	
		High flow support	17 (2.0)	45 (6.8)	
		Non-invasive	14 (1.6)	35 (5.3)	
		Invasive	16 (1.9)	54 (8.1)	
		(Missing)	62 (7.2)	5 (0.8)	
ICU/HDU admission	1459 (95.6)	No	744 (86.2)	528 (79.6)	<0.001
		Yes	59 (6.8)	128 (19.3)	
		(Missing)	60 (7.0)	7 (1.1)	
Inotrope	1360 (89.1)	No	729 (84.5)	602 (90.8)	0.002
		Yes	7 (0.8)	22 (3.3)	
		(Missing)	127 (14.7)	39 (5.9)	
Total PEWS	1427 (93.5)	Median (IQR)	2.0 (1.0 to 4.0)	2.0 (1.0 to 5.0)	0.001
PEWS over 2	1427 (93.5)	No	447 (51.8)	346 (52.2)	0.102
		Yes	329 (38.1)	305 (46.0)	
		(Missing)	87 (10.1)	12 (1.8)	
Length of stay	1301 (85.3)	Median (IQR)	2.0 (1.0 to 3.0)	3.0 (1.0 to 6.0)	<0.001

Supplementary Table L. *Treatments received stratified by comorbidity (excluding patients with asymptomatic or incidental SARS-CoV-2 infections and those with Multisystem Inflammatory Syndrome in Children (MIS-C)). ICU = intensive care unit. HDU = high dependency unit. PEWS= Paediatric Early Warning Score at presentation.*

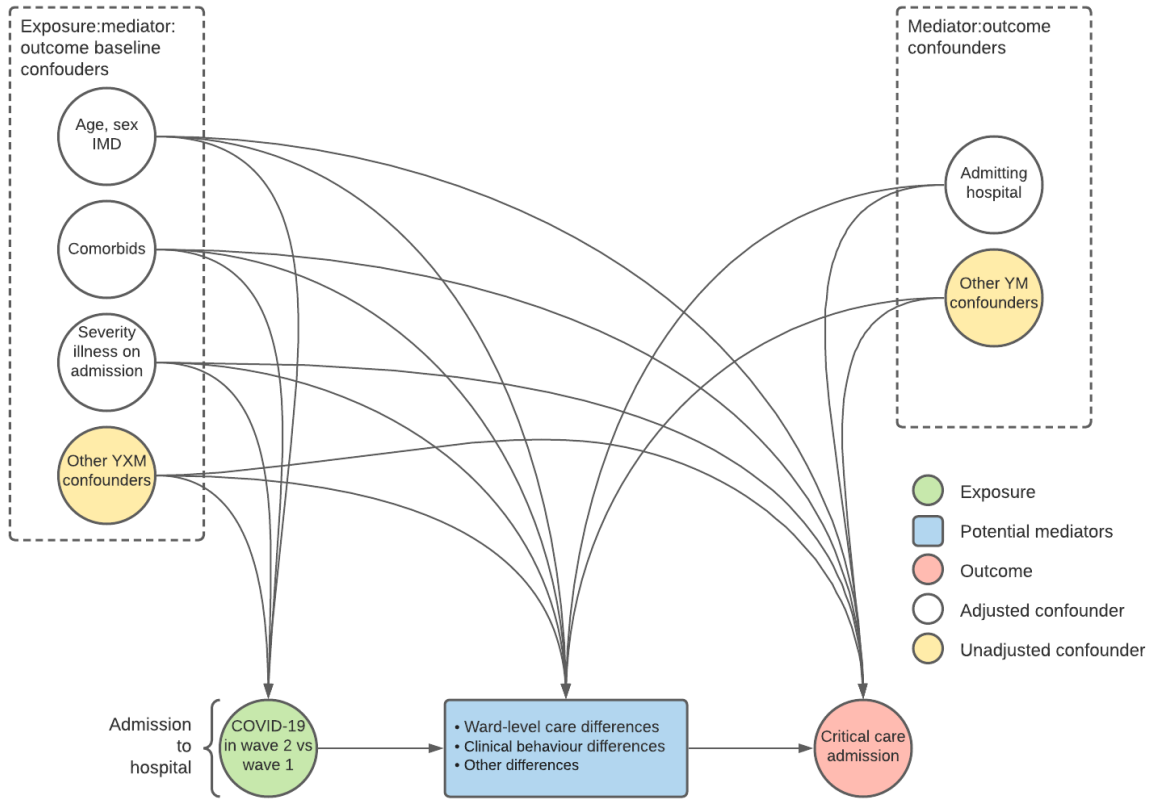
		Asympto / Incidental	Symptomatic	p
Total N (%)		427 (21.7)	1540 (78.3)	
Age at assessment (Years)	Median (IQR)	11.2 (1.5 to 15.9)	5.3 (0.4 to 14.2)	<0.001
Age	<1 mth	30 (7.0)	111 (7.2)	<0.001
	>1mth <1 y	54 (12.6)	399 (25.9)	
	1-4 y	64 (15.0)	246 (16.0)	
	5-9 y	49 (11.5)	182 (11.8)	
	10-14 y	85 (19.9)	263 (17.1)	
	15-19 y	145 (34.0)	339 (22.0)	
Sex at Birth	Male	214 (50.1)	826 (53.6)	0.224
	Female	212 (49.6)	712 (46.2)	
	(Missing)	1 (0.2)	2 (0.1)	
Ethnicity	White	240 (56.2)	778 (50.5)	0.172
	Black	27 (6.3)	100 (6.5)	
	South Asian	56 (13.1)	218 (14.2)	
	Other ethnic minority	51 (11.9)	237 (15.4)	
	(Missing)	53 (12.4)	207 (13.4)	
IMD quintile	1 (most deprived)	120 (28.1)	515 (33.4)	0.947
	2	75 (17.6)	299 (19.4)	
	3	55 (12.9)	219 (14.2)	
	4	47 (11.0)	188 (12.2)	
	5 (least deprived)	44 (10.3)	203 (13.2)	
	(Missing)	86 (20.1)	116 (7.5)	
Potential hospital acquired SARS-CoV-2	No	374 (87.6)	1475 (95.8)	<0.001
	Yes	53 (12.4)	65 (4.2)	
Total PEWS	Median (IQR)	1.0 (0.0 to 2.0)	2.0 (1.0 to 4.0)	<0.001
Any comorbidity	No/Unknown	208 (48.7)	867 (56.3)	0.006
	Yes	219 (51.3)	673 (43.7)	
Alternative reason for admission	No / Unknown	295 (69.1)	1458 (94.7)	<0.001
	Yes	132 (30.9)	82 (5.3)	

Supplementary Table M. *Demographics and key clinical characteristics of children with asymptomatic or incidental SARS-CoV-2 infections compared to those who were symptomatic. Column percentages by subgroup. IMD = Indices of multiple deprivation. PEWS= Paediatric Early Warning Score at presentation. IQR = Interquartile range*

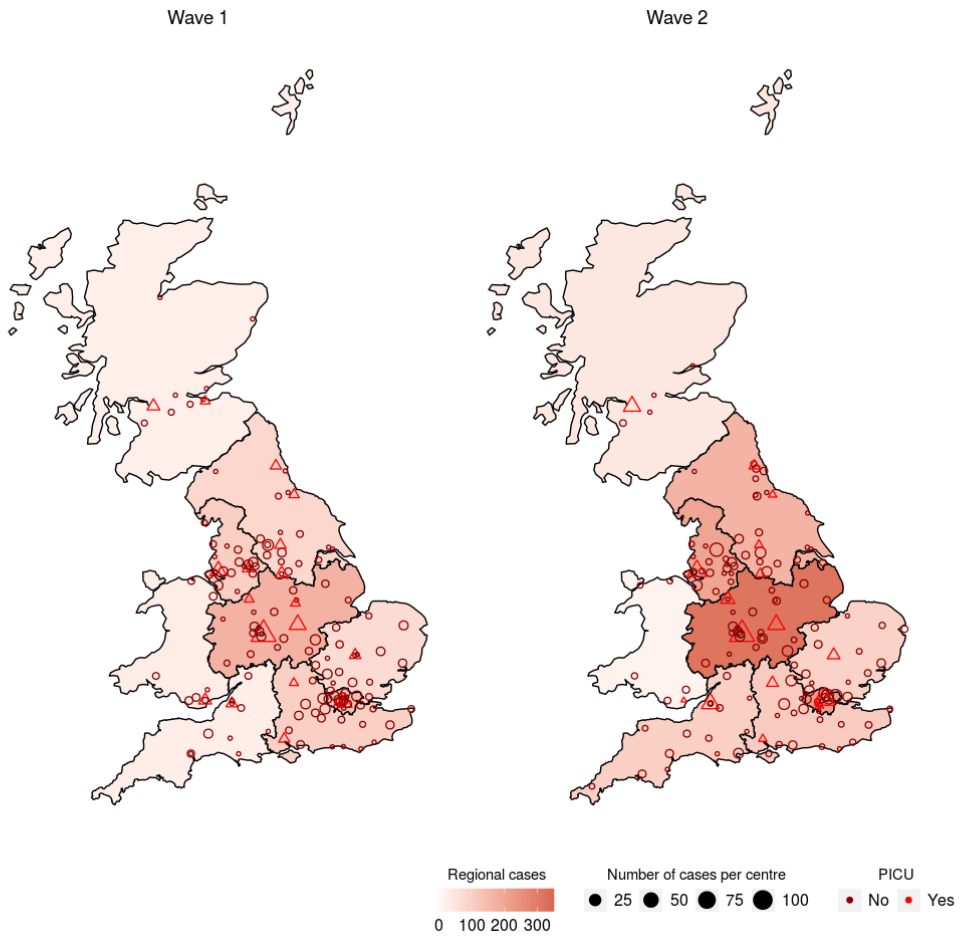
Supplementary Figures



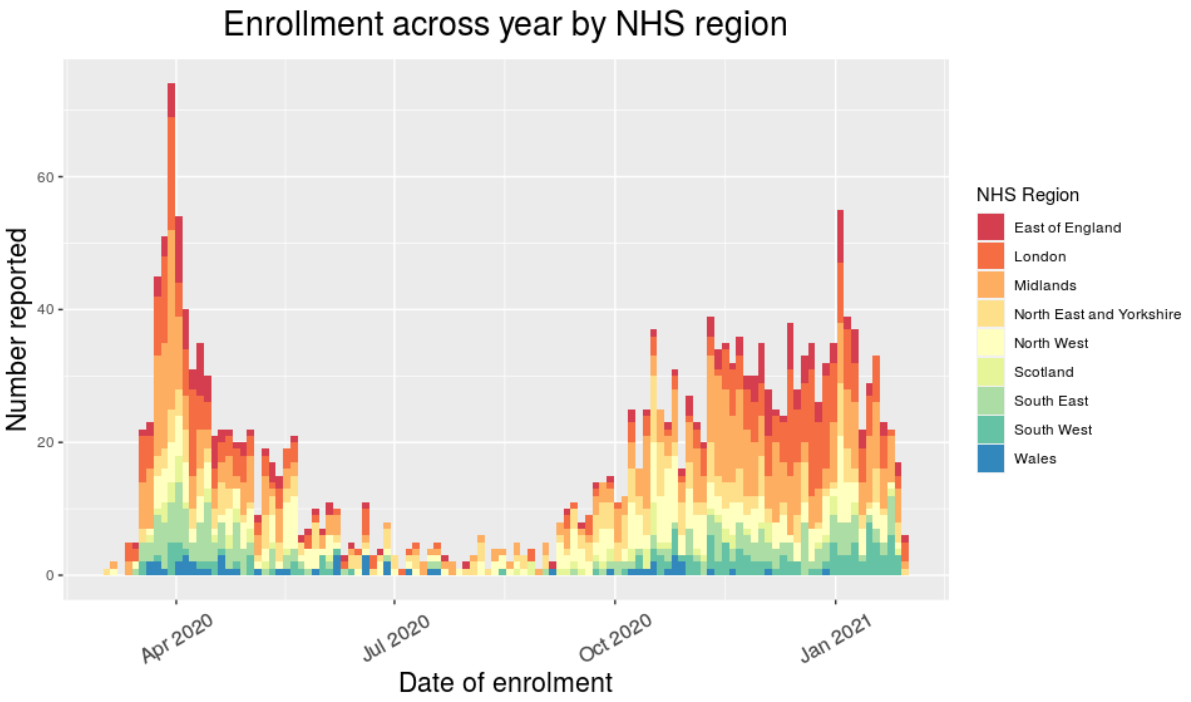
Supplementary Figure A. *Timeline of major lockdown events in England against SARS-CoV-2 admissions for patients under 18 years across England (admissions data from NHS England).[4] Magenta = face to face learning, purple = distance learning, pink = school holidays. This ISARIC4C analysis spans the period indicated by a white background. (NB. ISARIC-4C also includes data from Scotland and Wales)*



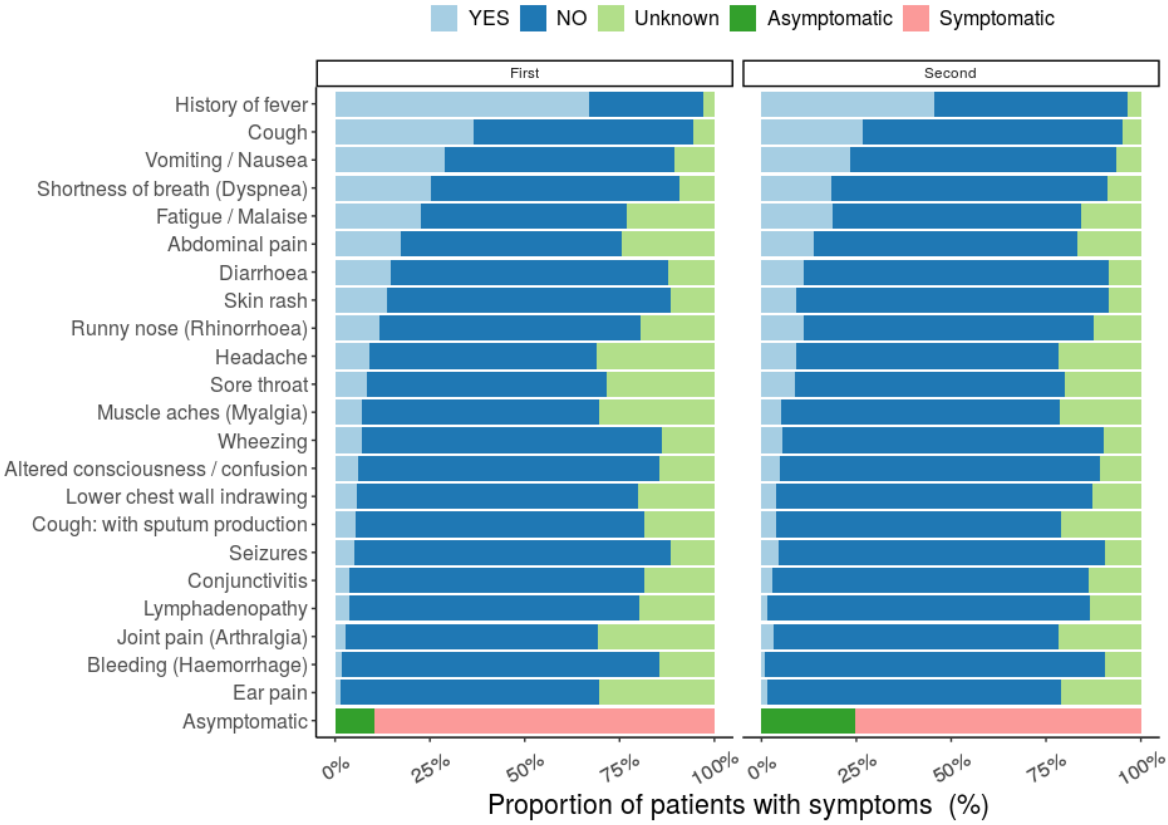
Supplementary Figure B. *Directed acyclic graph of factors associated with critical care admission for construction of multivariable analysis*



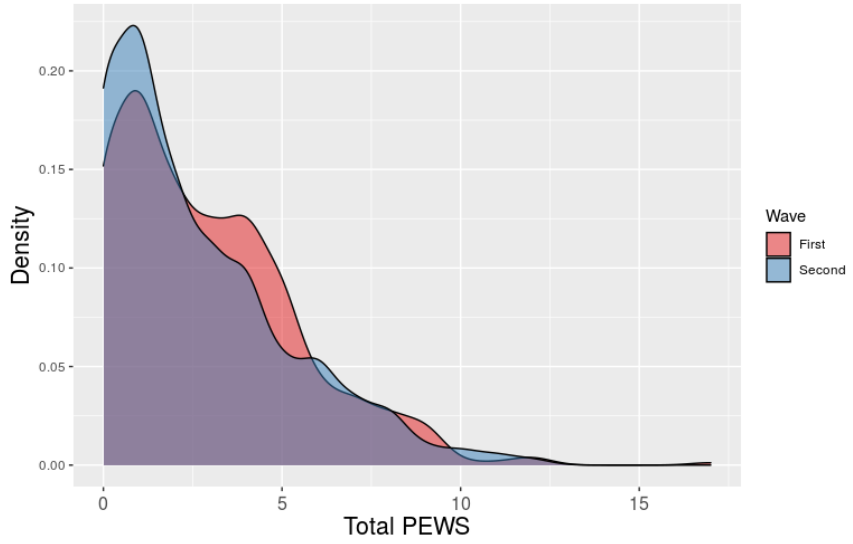
Supplementary Figure C. Map of sites of patient enrolment and cases by site. Sites with access to an onsite PICU are represented with triangles and those without as circles.



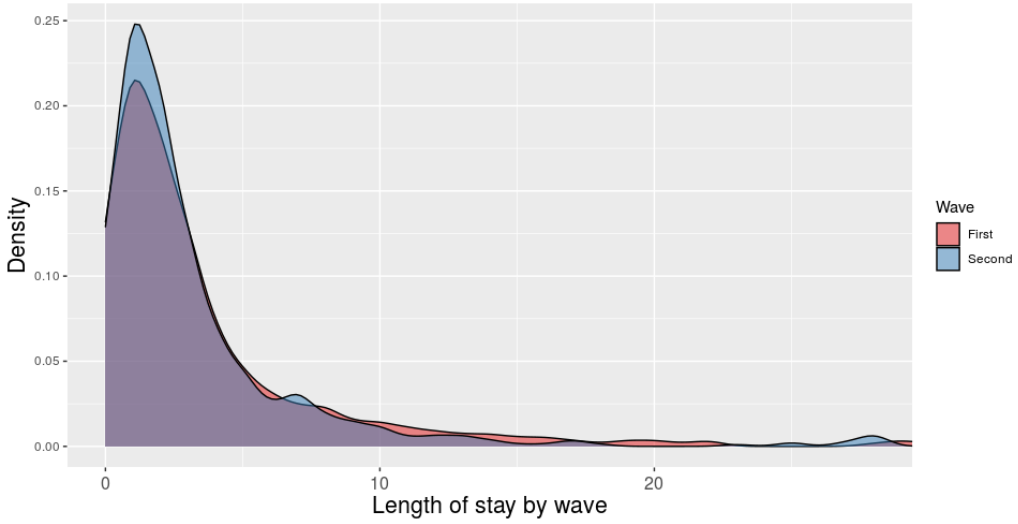
Supplementary Figure D. *Reporting of patients <19 years to ISARIC4C by NHS region. Regional peaks can be seen in November in the Midland (orange) and London in December (dark orange). These peaks closely mirrored those reported by Public Health England at the same time points.*[3]



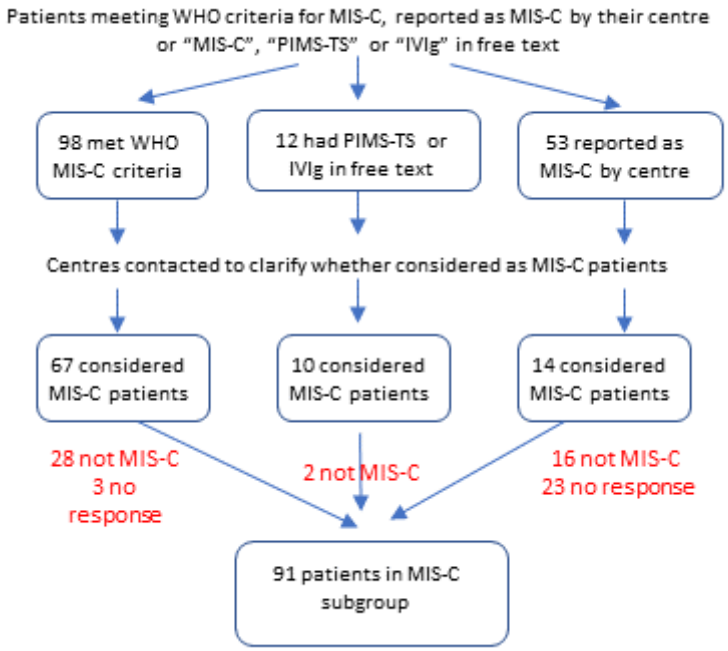
Supplementary Figure E. *Comparison of symptoms at presentation (whole cohort analysis).*



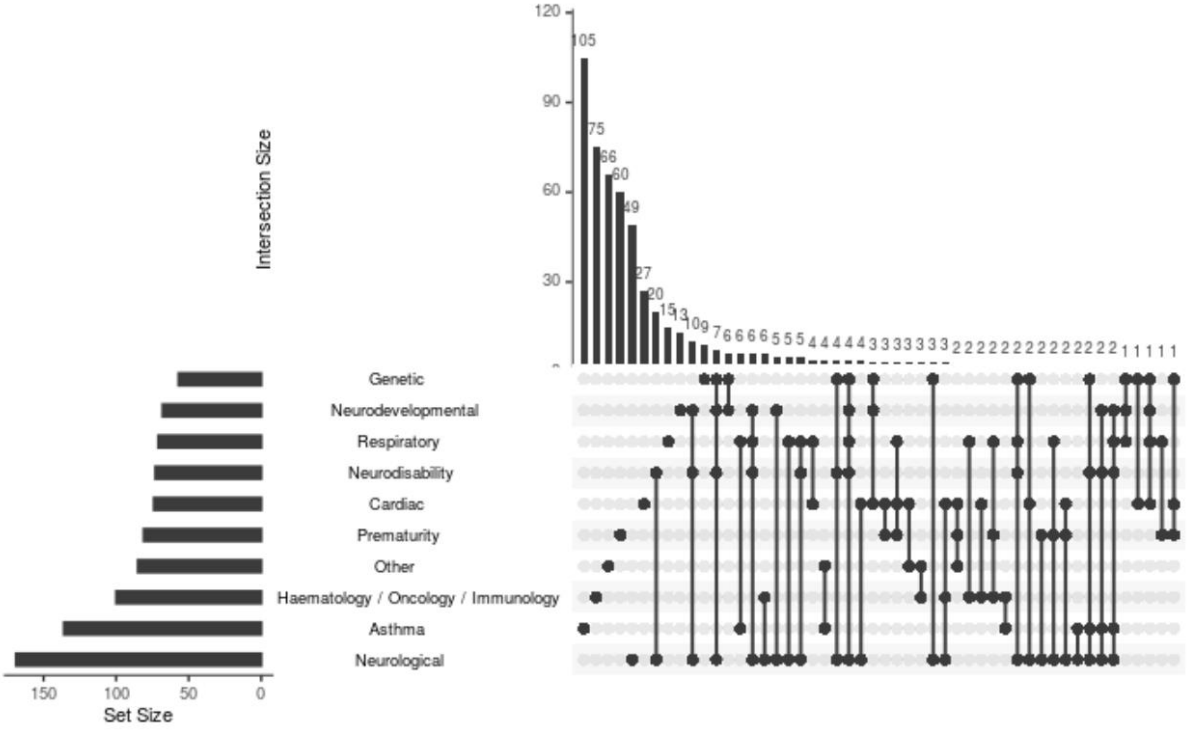
Supplementary Figure F. Paediatric Early Warning Score (PEWS) at presentation compared across the two waves (asymptomatic or incidental SARS-CoV-2 infections and patients with MIS-C excluded).



Supplementary Figure G. Length of stay compared across the two waves (asymptomatic / incidental SARS-CoV-2 infections and patients with MIS-C excluded)



Supplementary Figure H. Flowchart for indentification of patients with multisystem inflammatory syndrome (MIS-C). WHO = World Health Organisation, PIMS-TS = Paediatric Multisystem Inflammatory Syndrome – Temporally Associated with SARS-CoV-2, IVIg = Intravenous immunoglobulin.



Supplementary Figure I. UpSet plot of patients comorbidities in patients admitted to critical care (excluding asymptomatic and incidental SARS-CoV-2 infections). Plot represents a visualisation of set intersections in the data.

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2.Swann OV, Holden KA, Turtle L, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. *BMJ* 2020; **370**: m3249.

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